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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/364,847	07/30/1999	OLIVER P. PEOPLES	MBX030	9982

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/364,847	Applicant(s) PEOPLES ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

The request filed on 11/01/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/364,847 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-6 are pending in the application.

Amendment of claim 1 in Paper No. 13, filed 01/22/02 is acknowledged.

The examiner has previously requested references listed on Form PTO-1449 (see Paper No. 10). These references have not been received by the examiner and cannot be considered as requested. In order to ensure delivery of the IDS references to the examiner, it is suggested that applicants have the references hand delivered to the Group and have the receptionist contact the examiner upon arrival. The references will be fully considered upon receipt and Form PTO-1449 will be returned in a subsequent communication.

It is noted that claim 1 of Paper No. 18 is present in two different versions. In a conversation with Patrea L. Pabst on 02/19/02, Ms. Pabst indicated that claim 1 with the amendment, ", and wherein the fusion protein is under the control of a single promoter resulting in expression of both catalytically active E1 and E2" is the intended claim amendment. The claim has been examined accordingly.

Specification/Informalities

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Fusion Enzymes Catalyzing Successive Reactions of the Polyhydroxyalkanoate Pathway". See MPEP § 606.01.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 1 (claims 2-6 dependent therefrom) is confusing in the recitation of "the fusion protein is under the control of a single promoter" as promoters control protein expression and not protein activity. It is suggested that applicants replace the term with, for example, "expression of the fusion protein is under the control of a single promoter".

4. Claims 1 and 2 are rejected because of the recitation of "β-ketothiolase" in claim 1 and "beta-ketothiolases" in claim 2. It is suggested that applicants maintain consistency in the use of the terms by replacing ""β-ketothiolase" with "beta-ketothiolase" in claim 1 or replacing "beta-ketothiolases" in claim 2 with ""β-ketothiolases".

5. Claim 2 is confusing in the recitation of "phaP and phaC (1D)". It is suggested that the term be replaced with, for example, "phaP and phaC".

6. Claim 4 is unclear in the recitation of "wherein the linker is glycine-serine". It is unclear as to whether the term is meant to be interpreted as a linker comprised of glycine and serine residues or if the linker is a two-amino acid linker of glycine-serine. It is suggested that applicants clarify the meaning of the claim. The examiner has interpreted the claim as being a linker comprised of glycine and serine residues. If the examiner's interpretation of the claim is incorrect, applicant should so state and clarify the record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the

requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1-3, 5, and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Srienc (US Patent 6,143,952). Claims 1 and 2 are drawn to a protein fusion of the polypeptides as encompassed by claims 1 or 2 with or without a peptide linker, wherein expression of the fusion protein is under the control of a single promoter resulting in expression of catalytically active polypeptides. Claim 3 is drawn to a linker of between zero and 50 amino acids linking individual enzymes and claims 5 and 6 are drawn to expression of the fusion protein in a plant or bacteria, respectively. It is noted that the examiner has interpreted a linker of n (claim 1) or zero amino acids (claim 3) as being a fusion protein without a linker and therefore, the cited reference need not teach a peptide linker joining individual enzymes.

Srienc teaches (column 12) a plasmid, pPT700 (Figure 3) containing genes encoding beta-ketothiolase, acetoacetyl-CoA reductase, and a PHA polymerase, all operably linked to a single promoter. Srienc teaches (column 24) a multifunctional enzyme fusion protein, which is the product of a fusion of genes encoding beta-ketothiolase and acetoacetyl-CoA reductase and teach that such a fusion enzyme will have significant kinetic advantages in PHA synthesis. Srienc teaches (column 24) that a beta-ketothiolase and acetoacetyl-CoA reductase fusion enzyme can be expressed in E. coli. Srienc further teaches (column 7) that a PHA polymerase, encoded by phaC, may be part of a bifunctional or multifunctional enzyme and suggest that it may be a part of a larger fusion protein containing, for example, one or more additional enzymes involved in the PHA biosynthetic pathway. Srienc teaches (columns 9 and 10) that such a fusion protein can be expressed in a plant cell or tissue. This anticipates claims 1-3, 5, and 6 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Srienc in view of Bulow (Trends Biotech 9:226-231, 1991) and Argos (J Mol Biol 211:943-958, 1990). Claim 4 further limits the fusion protein of claim 1 to a linker of glycine and serine residues.

Srienc discloses the teachings as described above. Srienc does not teach a linker of serine and glycine residues.

Bulow teaches that the individual enzymes of a fusion enzyme are optimally linked by a short peptide linker (page 230, left column).

Argos teaches (page 947) advantages of using a glycine-serine oligopeptide linker peptide. Such advantages include flexibility of the linker provided by glycine due to its relatively small side chain, conformational and energetic stability due to hydrogen bonding of the polar side chain of serine with solvent in an aqueous environment and reduced susceptibility to of a glycine-serine oligopeptide linker to proteolysis.

Therefore, it would have been obvious to one of ordinary skill in the art for the fusion protein of Srienc comprising a linker of serine and glycine residues connecting the individual enzymes. One would have been motivated for a linker of glycine and serine linking individual enzymes to generate the fusion enzyme of Srienc because of the teachings of Bulow and Argos as described above. One would have a reasonable expectation of success for the fusion protein of Srienc comprising a linker of serine and glycine residues connecting the individual enzymes because of the results of Srienc, Bulow, and Argos. Therefore, claim 4, drawn to a fusion protein with a linker of serine and glycine residues as encompassed by the claim would have been obvious to one of ordinary skill in the art.

Applicants argue that the combination of the cited references of Bulow, Argos, Peoples (1987), Peoples (1989), and Somerville would not provide one of ordinary skill in the art with a reasonable expectation of success for the claimed fusion protein based on the following: 1) no naturally-occurring

fusion proteins as encompassed by the claims have been identified; 2) the enzymes comprising the claimed fusion proteins are large with uncharacterized active sites; 3) although the genes encoding individual enzymes of the PHA biosynthetic pathway had been cloned, no prior art reference discloses the construction of a fusion protein as encompassed by the claims; 4) enzymes of the PHA biosynthetic pathway interact with substrates and are found bound to the polymer granules. Applicants argue that one of skill in the art would have expected fusion proteins as encompassed by the claims to result in aggregates of large non-functional complexes and therefore, would have no reasonable expectation of success for generating said fusion proteins. Applicants' arguments are not found persuasive. The examiner has applied a previously uncited prior art reference, thus rendering the arguments against the references of Peoples (1987), Peoples (1989), and Somerville moot as the currently cited prior art reference of Srienc clearly recites fusion proteins as claimed by applicants. Furthermore, claims 1-3, 5, and 6 are now rejected under 35 USC 102(e) and a reasonable expectation of success for making the claimed invention need not be shown for a rejection under 35 USC 102(e).

Applicants argue that Bulow does not specifically teach a fusion of the enzymes recited in either of claims 1 or 2. As stated above, the currently cited prior art reference of Srienc teaches the claimed fusion proteins. Applicants further argue that the reference of Argos is not predictive of the claimed fusion proteins and further argue that one of ordinary skill in the art would not conclude that the linkers of Argos could be incorporated into a fusion enzyme without further experimentation. Applicants' arguments are not found persuasive. Peptide linkers are well known to one of ordinary skill in the art and, based on the teachings of Srienc and Argos as described above, one of ordinary skill in the art would have had a reasonable expectation of success for generating a fusion protein as encompassed by the claims with a peptide linker of glycine and serine residues.

Conclusion

9. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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